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Gene Therapy: Beyond 2000

"Success in gene therapy, at last" (*New York Times* editorial headline, April 30, 2000). Such heartening news is a joy to behold for practitioners of the science of gene therapy. Ever since the news of the death of 18-year-old Jessie Gelsinger 9 months ago, the field of gene therapy has witnessed an unprecedented barrage of bad publicity. Sweeping statements like "The end of a promising medical technology," "A promise unfulfilled," or "Undue hype leads to premature end" were the rule rather than the exception. The general condemnation of the field was not restricted to the news media; many prominent scientists and research establishments also expressed deep concern. Interestingly, the commercial sector involved in gene therapy reacted to the adverse publicity with indifference and even defiance on Wall Street.

The Senate health subcommittee had a hearing on gene therapy safety and risks. A follow-up is in the offing in the coming weeks. Additionally, the House of representatives is planning to have a hearing on this subject, and both the Secretary of Health and Human Services and the President have commented on the adverse effects of gene therapy. Not surprisingly, there has been a flurry of activity at the NIH and the FDA with very active participation from the American Society of Gene Therapy. The gene therapy community is now bracing itself for new regulations and requirements for clinical trials. We hope that these new guidelines will be sensible and practical and not adversely affect the current steady progress in the field of gene therapy.

The basic concept of gene therapy has always been very simple—introduce a gene whose product has the ability to either cure or slow down the progression of disease. The recent paper by Alain Fischer and colleagues from Paris (*Science* **288**: 669–672, 2000) has brought this simple concept to reality. Two infants, aged 11 and 8 months, who suffered from severe combined immunodeficiency (SCID)-X1 disease have been successfully treated for over 270 days. A third child treated at 1 month of age is at home without any other therapy for over 4 months.

SCID-X1 is an x-linked inherited disorder characterized by an early block in T and natural killer (NK) lymphocyte differentiation due to mutations of the gene encoding the γc cytokine receptor subunit common to IL-2, -4, -7, -9, and -15 receptors. A mutation in the γc subunit leads to disruption of signals for growth, survival, and differentiation to lymphoid progenitor cells. CD34+ cells from the patient were transduced *ex vivo* with a recombinant murine leukemia viral vector containing the γc receptor gene and infused back into the young patients without any chemoablation. After 10 months γc transgene expression in T and NK cells was detected in both patients, but more importantly T, B, and NK cell counts and function were comparable to those of age-matched controls. To all appearances, the recipients are clinically cured, and the fantastic promise of gene therapy is realized!

Several caveats clearly remain—(i) only 10 months of data are available, and expression of the transgene driven by LTRs may cease; (ii) a very small number of patients have been treated to date; and (iii) as the authors point out, this success may be due to strong positive selective pressure provided to the corrected lymphoid progenitors. What is particularly gratifying, however, is the care and caution exercised by these investigators, involving years of experimentation in mice and dogs and incremental use of the technical advances in the field.

The news of successful gene therapy in SCID-X1 patients was preceded with guarded optimism about the success in two hemophilia patients receiving human factor IX genes delivered by adeno-associated viral vectors (Kay *et al., Nat. Genet.* **24**: 257–261, 2000). Although there is much to cheer about in these early successes, we must also remind ourselves that "a single sparrow does not make spring."

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